Presentation type:
Platform, Poster

Track:
Aquatic Toxicology and Ecology

Session:
A Systems Biology Approach to Predictive Ecotoxicology

Abstract Title:
Androgen receptor mediated compensation of estradiol in response to aromatase inhibition: a mathematical model

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Abstract:
Chemicals in the environment have the potential to cause reproductive toxicity by acting on the hypothalamus-pituitary-gonadal (HPG) axis. We have developed a mathematical model to predict chemical impacts on reproductive hormone production in the highly conserved HPG axis using the fathead minnow (*Pimephales promelas*). The HPG axis controls the supply of reproductive hormones available to the body through feedbacks between local hormone levels and enzymes produced in response to changes in gene expression. This behavior has been recently observed in studies of fathead minnow exposed to the highly selective aromatase inhibitor fadrozole. In these studies, the enzyme-mediated transformation of testosterone into estradiol, strongly correlated with egg production (oogenesis), is initially inhibited by fadrozole. However, over time direct inhibition of aromatase by fadrozole is offset, by induction of several central steroidogenic (cytochrome p450) enzymes critical to estradiol biosynthesis. The biochemical mechanisms mediating this apparent compensatory gene expression have not been fully characterized. However, microarray-based gene expression studies conducted by our group suggest the androgen receptor mediates may mediate these compensation pathways. Here we develop a mechanistic mathematical model, grounded in experimental data, to test these compensation hypotheses. Parameterized using data primarily from qPCR and literature sources, this model reproduces gene-based induction events that drive *de novo* aromatase production and associated increases in estradiol production at lower fadrozole doses (3 ug/L), but predicts decreased reduced capacity for compensation at higher doses (30 ug/L) despite further gene expression increases, consistent with current experiments,. Extensions of this predictive model to other less selective aromatase inhibitors (e.g., ketoconazole) will be discussed.

STICs Field	Entry
1 – Influence/profile	Not applicable
2 – Clearance tracking no.	Assigned automatically
3 – Principal Investigator / Project Officer	Michael Mayo (non-EPA PI) if you have to list an EPA employee – Dan Villeneuve
4- Product title	Copy and paste from abstract
5 - Authors	See abstract See below for non-epa e-mail addresses
6a- Product type	Presentations and technical summaries
6b-Product subtype	Abstract
6c – Records schedule	Not a senior official
7a – Impact statement	n/a
7b- Product description	Paste in abstract
8 – Bibliographic citation	SETAC North America 33rd Annual Meeting, 11-15 November, Long Beach, CA, USA.
9 - Access	Public
10 – Tracking and Planning Task	2.2.3 2.2.3: Systems models linking reproductive and neurodevelopmental effects to endocrine disruption
10 – Tracking and Planning Product	3) Development of a computational (in silico) systems model that simulates key aspects of a chemicals potential to disrupt normal HPG axis regulation, linking changes in key events within adverse outcome pathways (chemicals selected from EDSP21).
11 – Copyright permission	No
12 - QA	not applicable
13 – Policy implications	No
14 - Keywords	model hypothalamic-pituitary-gonadal axis endocrine disruption fish

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